Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested.

By the present amendment, claims 28-39 have been added. Support for amended claims 28-39 can be found at ¶¶0092-0118 of the present application.

Below is a discussion of the 35 U.S.C. §112, first paragraph, rejection of claims 4, 6-8, 15, and 26-27.

1. 35 U.S.C. §112, first paragraph, rejection of claims 4, 6-8, 15 and 26-27.

Claims 4, 6-8, 15, and 26-27 are rejected under 35 U.S.C. §112, first paragraph, "because the specification fails to provide an enablement for the full scope of the claimed invention". The Office Action argues that Kerbel, *Cancer & Metastasis Rev*. 17:301-304, 1999 (hereinafter, "Kerbel"), Vieweg *et al*., *Cancer Investig*. 13(2):193-201, 1995 (hereinafter, "Vieweg"), and Hoffman, *Invest. New Drugs* 17:343-360, 1999 (hereinafter, "Hoffman") teach that the heterotopic subcutaneous xenotransplantation of cell lines in an immunodeficient nude mouse fails to reflect human carcinoma and, therefore, a person of skill in the art would need to carry out further experimentation to be effective in inducing apoptosis in human epithelial carcinoma *in vivo* or treating a subject with prostate cancer or breast cancer. Referring to Wang *et al*., *Eur. J. Physiol*. 448:274-286, 2004 (hereinafter, "Wang"), the Office Action additionally argues that a person of skill in the art would need to engage in further experimentation to resolve the paradox outlined in Wang, especially since a tumor mass generally contains a heterogeneous population of cells at different stages of cancer progression.

Applicants respectfully submit that the amount of direction or guidance disclosed in the present specification is sufficient to enable the skilled artisan to make and use the method recited in claims 4, 6-8, 15, and 26-27 using only routine experimentation.

"[T]o be enabling, the specification...must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Id.* at 1561 (emphasis added), *quoted in Genentech, Inc. V. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. V. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999). Some experimentation, even a considerable amount, is not "undue" if, *e.g.*, it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Facts that should be considered in determining whether a specification is enabling include: (1) the quantity of experimentation necessary to practice the invention; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988).

Claim 4 recites a method for inducing apoptosis in human prostate cancer or breast cancer cells. The method includes delivering to and expressing in the cells a nucleic acid comprising (i) a nucleotide sequence encoding human KChAP protein and (ii) a promoter active in the cancer cells. The promoter is operably linked to the sequence encoding the protein, and the cancer cells are in a tumor of a subject. The nucleic acid is in a viral vector, which is delivered to the cancer cells by intratumoral injection.

The specification of the present application provides guidance and direction to the skilled artisan commensurate with the scope of the claims. The specification of the present application teaches that apoptosis can be induced in prostate cancer cells or breast cancer cells by delivering and expressing a nucleic acid encoding human KChAP protein (in a viral vector) via intratumoral injection. The specification notes that the present method is especially useful for treating a patient with an epithelial carcinoma, such as breast cancer or prostate cancer (¶0047). For example, the specification notes that apoptosis may be induced in cancer cells, particularly prostate cancer cells, by introducing a KChAP protein in the cell (¶0070). The specification also notes that polynucleotides comprising a coding sequence for KChAP protein can include a promoter that permits expression of the protein (¶0062). Additionally, the specification notes that viral vectors may be used to deliver the KChAP polynucleotide to the cell (¶0063). Further, the specification notes that delivery of the KChAP polynucleotide may be via intratumoral injection (¶0075).

The specification of the present application also includes several working examples demonstrating that delivery and expression of a nucleotide sequence

encoding human KChAP protein induces apoptosis in human prostate cancer and breast cancer cells. Example 1 of the specification demonstrates that delivery and expression of a nucleotide sequence encoding KChAP induces apoptosis in LNCaP cells, which are a prostate cancer cell line containing native p53 protein. Example 2 of the specification demonstrates that delivery and expression of a nucleotide sequence encoding KChAP induces apoptosis in Du145 cells, which are a prostate cancer cell line containing mutated p53 protein. Example 3 of the specification demonstrates that *in vivo* growth of subcutaneous implants of human prostate cancer cells is inhibited by increasing intracellular levels of KChAP. Example 4 of the specification demonstrates that delivery and expression of a nucleotide sequence encoding human KChAP protein induces apoptosis in mammary epithelial cancer cells (*i.e.*, MCF-7 cells). Taken together, Examples 1-4 demonstrate that delivery and expression of a nucleotide sequence encoding human KChAP protein induces apoptosis in both prostate cancer cells and breast cancer cells.

Additionally, the Office Action provides no evidence to doubt the veracity of the objective statements made in the specification. It is well established that "[t]he Examiner has the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A requirement for some experiment does not prevent the satisfaction of the enablement requirement. *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1329 (Fed. Cir. 1990). The Federal Circuit has made it clear that "[w]hen rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a

reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, *providing sufficient reasons for doubting any assertions* in the specification as to the scope of enablement." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1561-1562 (Fed. Cir. 1993) (emphasis added).

Specifically, the Office Action has not provided any factual evidence to show a reason to doubt the objective truth of Applicants' statements, which must be relied upon for enabling support; namely, that delivery and expression of a nucleotide sequence encoding human KChAP protein can induce apoptosis in human prostate cancer or breast cancer cells.

The Office Action identifies Kerbel, Vieweg, and Hoffman in support of its argument that the animal model exemplified in the present specification does not sufficiently represent clinical cancer, especially with regard to metastases and drug sensitivity. Applicants fail to see the relevance of this argument because the claimed method is not directed to treating clinical cancer. "Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.,* 349 F.3d 1333, 1338 (Fed. Cir. 2003). *See also In re Cortright,* 165 F.3d 1353, 1359 (Fed. Cir. 1999) (claims to method of "restoring hair growth" encompassed achieving full head of hair, but did not require it).

The present claims are directed to inducing apoptosis in human prostate cancer or breast cancer cells. Although it is true that the present application

contemplates treating a variety of cancers by induction of apoptosis, practicing the claimed invention does not require the treatment of clinical cancer. Claims 4, 6-8, 15, and 26-27 are thus enabled because the Office Action has not provided any basis in evidence or fact that doubts the beneficial effects of inducing apoptosis in human prostate cancer or breast cancer cells following delivery and expression of a nucleotide sequence encoding human KChAP protein.

With respect to the animal model exemplified in the present application, the Office Action relies on Kerbel for the propostion that "orthotopically transplanted tumors do not necessarily recapitulate the 'encouraging' responses from their ectopically (usually subcutaneous) grown counterparts." Kerbel states that "[i]t is not possible to predict at this time how general and reproducible this kind of result is since few laboratories use orthtopic transplantable models for *in vivo* drug testing, especially in the case of cancers such as prostate and lung which, by definition, are harder to manipulate and monitor using orthotopic injection procedures" (p. 302, 2nd column). Thus, Kerbel actually teaches that the use of tumor models other than the one exemplified by the present application (*i.e.*, an orthotopic injection procedure) would be very difficult for studying prostate cancer.

The Office Action also relies on Vieweg for proposition that "the site of tumor implantation can greatly influence biological properties and immunological responsiveness to treatment." Vieweg is a review article discussing considerations for the use of cytokine-secreting tumor cell preparations for cancer treatment. The teaching of Vieweg appears to have been taken out of context. If one skilled in the art wished to create a vaccine against a tumor type, then it would be very important

to make sure that the tumor was located in the cite normally found (*i.e.*, orthotopically) because the immune response would not be representative otherwise. For example, colon cancer would have a different cytokine profile than brain cancer due to differences in inflammatory cell make-up. The present invention does not depend on the immune response for activity, so the teaching of Vieweg for cite specificity is not relevant.

The Office Action also identifies Wang in support of the argument that the apparent paradox that K^+ channels favor tumor cell proliferation while also promoting apoptotic cell death confounds the manipulation of K^+ function and/or expression as an option for the treatment of cancers. Once again, Applicants fail to see the relevance of this argument because the claimed method is not directed to treating cancers. Even if the present claims were directed to a method of treating cancers, a closer reading of Wang would not lead a skilled artisan to believe that further experimentation is needed to resolve the apparent paradox suggested by Wang when treating cancers. Wang also provides that K+ channels as a molecular target for gene therapy of cancers are possible. For example, "over-expression of K^+ channels by infection of tumour cells with virus vectors carrying K^+ channel cDNAs, will be feasible sooner or later" (p. 282, 1st column). Thus, "strategic use of K^+ channel modulation may be beneficial (p. 282, 1st column).

Moreover, the Office Action's apparent position that the specification cannot teach how to use the claimed method unless it teaches solutions to all the problems in the field of cancer therapy is contrary to controlling case law. *See, e.g., In re Brana,* 51 F.3d 1560, 1568 (Fed. Cir. 1995).

In B*rana,* the claims were directed to compounds disclosed as anticancer agents. *Id.* at 1562. The USPTO rejected the claims as non-enabled, *id.* at 1563-64, despite working examples in Brana's specification showing treatment of cancer in a mouse model. *Id.* at 1562-63. The USPTO argued that the results of the mouse testing "are not reasonably predictive of the success of the claimed compounds for treating cancer in humans." *Id.* at 1567. The court concluded that this position "confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *Id.* The *Brana* court held that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Id* at 1568.

Here, the claims are simply directed to a method of inducing apoptosis in human prostate cancer or breast cancer cells, and Applicants' specification provides several working examples demonstrating just that both *in vivo* and *in vitro*. The Examiner has discounted the specification's working examples because "the animal model exemplified in the instant specification, i.e. subcutaneously-growing human cell lines in immunodeficient mice, do[es] not sufficiently represent clinical cancer, especially with regard to metastasis and drug sensitivity". Enablement, however, includes an expectation of further research and development. Thus, enablement is not precluded even if the claims encompass methods, such as prostate and breast cancer therapy that have not yet overcome all the obstacles to their clinical use.

The Office Action has not established that undue experimentation would have been required to practice the *claimed* method; specifically, a method of inducing apoptosis in human prostate cancer or breast cancer cells. Therefore, the amount of direction or guidance disclosed in the specification is sufficient to enable the skilled artisan to make and use the methods of claims 4, 6-8, 15, and 26-27 using only routine experimentation.

Accordingly, Applicants respectively submit that claims 4, 6-8, 15, and 26-27 are enabled by the present application, and request that the 35 U.S.C. §112, first paragraph, rejection of these claims be withdrawn.

In view of the foregoing, it is respectfully submitted that the present application is in condition for allowance, and allowance of the present application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this matter to our Deposit Account No. 20-0090.

Respectfully submitted,

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